

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Amar Lulla, *et al.* § Group Art Unit: 1616
Serial No.: 10/518,016 § Examiner: Kristie Latrice Brooks
Filed: July 6, 2005 § Confirmation No.: 4912
For: COMBINATION OF AZELASTINE AND §
STEROIDS §

DECLARATION UNDER 37 CFR § 1.132

I, Geena Malhotra, hereby declare and say that:

1. I am a co-inventor of the invention claimed in the above-identified patent application.
2. Attached as Exhibit A is comparison data for five compositions:

Column 1: Azelastine.HCl

Column 2: Budesonide

Column 3: Azelastine.HCl & Budesonide

Column 4: Fluticasone Propionate

Column 5: Azelastine.HCl and Fluticasone Propionate

Table I of Exhibit A sets forth the ingredient list for the five compositions. Table II of Exhibit A sets forth comparative stability data for the five compositions. The results in Table II show the impurity levels in the initial compositions, and after storage under certain conditions: for example "25/60 RH at 1 M" means the composition was stored for one month at a temperature of 25 degrees C and at a relative humidity of 60. The results in Table II show that the individual active materials (e.g., azelastine.HCl, budesonide, and fluticasone

propionate) have good stability, in that the impurity levels are fairly constant in all the tests. The results in Table II also show that the combination of azelastine and budesonide are relatively unstable, with varying, and high amounts of impurities developing during the tests. Surprisingly, the results for azelastine and fluticasone show good stability throughout the tests, as the amount of impurity remains constant and at a low level.

3. Attached as Exhibit B is a compilation of statements from 6 medical practitioners, labeled B1-B6, along with typed transcriptions. As is self-evident, these statements attest to various advantages and superior results associated with patient use of the DUONASE product comprising azelastine and fluticasone.

4. A pharmaceutical formulation comprising azelastine and fluticasone is commercially available where approved as DUONASE nasal spray, as shown in attached Exhibit C containing information from the following website:

<http://www.cipladoc.com/therapeutic/admin.php?mode=prod&action=disp&id=213>.

5. Attached as Exhibit D are descriptions of the testing method used to generate the stability data discussed in Exhibit A. Exhibit D also states the nature of the impurities observed in the compositions described in Exhibit A and how those impurities were detected.

6. Based on my analysis of the entirety of data provided in the Exhibit A, I have concluded that the azelastine and fluticasone composition displays an unexpectedly beneficial stability when compared to the azelastine and budesonide composition.

7. I am unaware of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid.

8. The present application is licensed to Meda Pharmaceuticals.

9. I, Geena Malhotra, further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: September 23, 2010


Geena Malhotra

Comparative Composition data of Azelastine with steroids

Ingredients	Azelastine (%w/w)	Budesonide (%w/w)	Azelastine + Budesonide (%w/w)	Fluticasone (%w/w)	Azelastine + Fluticasone (%w/w)
Drugs	137 mcg	64 mcg	137 + 64 mcg	50 mcg	140 + 50 mcg
MCC+CMC (Avicel RC)	-	-	2.0	0.751.5	2.01.5
HPMC	0.10	-	-	-	-
Dispersible cellulose	-	1.25	-	-	-
Dextrose Anhy.	-	-	-	2.55.0	-
Anhy. Glucose	-	5.0	-	-	-
Glycerin	-	-	2.3	-	2.32.6
Polysorbate 80	-	0.016	0.005	0.0025.005	0.005025
BKC 40% w/w solution NF	0.0125	-	0.005	100.100.02	0.10
Phenyl ethyl alcohol	-	-	-	0.125	0.25
Pot sorbate	-	0.12	-	-	-
Disodium EDTA	0.05	0.01	0.01	-	0.01
Sodium Chloride	0.68	-	-	-	-
Citrate	0.048	-	-	-	-
Disodium Monohydrate	-	-	-	-	-
Disodium Phosphate	0.322	-	-	-	-
Hydrochloric acid	-	q.s.	-	-	-

Comparative Stability data of Azelastine with steroid Compositions

Stability tests	Azelastine	Budesonide	Azelastine + Budesonide	Fluticasone	Azelastine + Fluticasone
	INITIAL	INITIAL	INITIAL	INITIAL	INITIAL
Assay	100	97.6	98+97	101.6	100+101.12
PH	6.78	4.51	6.0	6.4	6.1
Total Impurity	0.03	0.26	$\leq 0.1 + 2.32 + 0.11$	0.52	$0.08 + 0.6$
	25/60 RH at 1M	25/60 RH at 1M	25/60 RH at 1M	25/60 RH at 1M	25/60 RH at 1M
PH	6.86	4.68	5.94	Not Done	Not Done
Total Impurity	0.12	0.25	$\leq 0.1 + 0.97 + 0.07$	Not Done	Not Done
	25/60 RH at 3 M	25/60 RH at 3M	25/60 RH at 3 M	25/60 RH at 3 M	30/65 RH at 3M
PH	6.76	4.6	5.96	6.21	5.85
Total Impurity	0.13	0.42	$\leq 0.1 + 5.39 + 0.16$	0.46	$0.2 + 0.84$
	40/75 RH at 1M	40/75 RH at 1M	40/75 RH at 1M	40/75 RH at 1M	40/75 RH at 1M
PH	6.86	4.69	5.92	6.35	5.82
Total Impurity	0.13	0.29	$\leq 0.1 + 5.53 + 0.05$	0.52	$0.4 + 0.89$
	40/75 RH at 3M	40/75 RH at 3M	40/75 RH at 3M	40/75 RH at 3M	40/75 RH at 3M
PH	6.76	4.61	5.91	5.98	5.81
Total Impurity	0.18	0.49	$\leq 0.1 + 18.29 + 0.23$	0.53	$0.37 + 0.85$

Dr. C. M. Mathew Chooracken

B. Sc., M. B. B. S., M. S. (E. N. T.) D. L. O.
Senior Specialist in E.N.T.
Civil Surgeon
District Hospital, Kottayam
Reg. No. 9473

Consultation:
Behind Margin Free Market
Near Kotayam East Police Station
Collectorate P.O., Kottayam - 686 002
Ph: 2564884, Mb: 9447288822

To Cepha Respiratory L

I have been using
the Deconase nasal spray
regularly for my nose and other
patients. I found it is
very effective when compa-
red to available other nasal
sprays. Oral medication
can be avoided as well.


Dr. C. M. Mathew Chooracken

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Civil Surgeon,
District Hospital, Kottayam
Reg. No. 9473

Kottayam
23/8/05

Dr. C.M.MATHEW CHOORACKEN

To Cipla Respiratory

I have been using the Duonase nasal spray regularly for my nasal allergic patients. I found it is very effective when compared the available other nasal sprays. Oral medication can be avoided as well.

Kottayam
23/8/05

Confidential

डॉ. पी. एन. टेजलकर
एम. एस. (ई.एन.टी.)
भारत, काल, गाला एवं वार्दन रोग विशेषज्ञ
पूर्व रजिस्ट्रार ई.एन.टी. हॉस्पिटल, जान्मे

विळिनिक	
गुजराती समाज, नई सड़क, उज्जैन मा 2561981	जब मेडिकल सोसायट (धासाबद्धा पेट्रोल पम्प के पास भांडापुर, कीणोल, उज्जैन मा 2514584
समय प्रातः 11 से 2.00	रात्रिवार अवकाश समय साथ 6 से 8.30

दिशेषक्षण

- बाक एवं सायनस इन्डोलोपी (दूरवीच छाए आपरेशन)
- माइक्रोलिंग्याल सर्जरी
- माइक्रोइनर सर्जरी (जर्सनी, प्राइ एवं एचीटजर्सोनड री प्राइक्षण प्राप्त)
- बाक की प्लास्टिक सर्जरी (राईगोस्टार्टी)

Regarding Dexamethasone

18.8.2008

Using this product for how many days

This is ideal, first line agent for the patient. The combination is adequate to deal with all types of allergy.

- Act on both phases (early as well as late phase of allergy ie inhibit)

- inhibition of H1 receptor activity & few side effects.

- Act on multiple receptors

The systemic bioavailability is less so care be taken for a long period without side effects.

Tough to allergy safe to H1

S

DR.P.N.TEJANKAR

M.S. (E.N.T)
E.N.T and Neck Specialist
Ex-Registrar E.N.T. Hospital, Bombay

CLINIC

Gujrati Samaj,
Nai Sadak, Ujjain
2561981
Time Mor: 11 to 2.00
SUNDAY

Jai Medical Centre (Near
Vasavda petrol pump)
Ghantaghari, Freegunj, Ujjain
2514884
Time.eve. 6 to 8.30
HOLIDAY

.....**Specialist.....**

• Nose and sinus endoscopy • Microlaryngeal Surgery • Microear Surgery (Trained from Germany, France and Switzerland) • Plastic Surgery of the Nose (rhinoplasty)

.....

Regarding Duonase

Using this product for last so many days. This is ideal, first line agent for the patient. The combination is adequate to deal with all type of allergy.

- Acts on both phases (early as well as late phase of allergy i.e. inhibit)
- Antagonises the H1 receptor activity with few side effect.
- Acts on multiple symptoms.
- The systemic bioavailability is less so can be used for a longer period without side effect.

Tough to allergy safe to Nose

DR. PRASAD JAWALEKAR M.S (E.N.T)

Reg.no.071882

E.N.T Specialist

Krishna General Hospital

Dhanvantari E.N.T.Hospital

Gavhane building, P.C.M.T Chowk,

Khodad Road, Narayangaon,

Bhosari,Pune 411039. ☎ 27129516

Taluka Junnar, Dist. Pune 410504

Time: eve. 5-00 to 8-00

SUNDAY CLOSED ☎ 02132-(Hosp.)244766 (R)243969

I have prescribed "Duonase Nasal spray" for 258 patients since Aug 2004 to Aug 2005. And I found that Duonase Nasal Spray very very effective in all types of allergic rhinitis. Especially in "Seasonal allergic rhinitis", Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both i.e. "Duonase Nasal Spray".

So I hereby strongly recommend Duonase Nasal Spray for allergic rhinitis.

Confidential

No: 25469



Dr. Manish Manjal

M.B.B.S., M.S. Diploma of National Board (ENT), M.N.A.M.S.
D.H.A., D.N.D., D.N.A., D.T.M., D.M.S.

EAR - NOSE - THROAT AND HEAD-NECK SURGEON

Consultant Otorhinolaryngologist & Head-Neck Surgeon
Dayanand Medical College & Hospital, Ludhiana
Formerly Consultant Christian Medical College
and Hospital, Ludhiana.

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Clinic-cum-Residence
52-C, Udam Singh Nagar,
Adj. P.A.U. Gate No.4,
Next to Lions Bhawan, Ludhiana

Dr.

Pt.

Pr.

Lo.

Rin.

Wat.

Op.

St.

D.

D.

D.

I have been using nasal sprays from the year 1993, ever since I joined my ^{Asst. Prof.} present institution. I have used beclomethasone, budesonide, Azelastine, fluticasone, mometasone, with oral anti-histamines. Treatment down the line till date.

The present combination spray of a weak (non-sedating component) Azelastine and fluticasone (steroidal component) is comparable by itself in my patients of chronic simple rhinitis; following nasal sinus polypsis surgery and those unwilling to undergo the surgery or unfit for surgery.

There is a response noted within a week in a few patients but the maximum

consultation: Evening 8.30 P.M. to 9.30 P.M. & 8.30 P.M. to 1.30 P.M.
Morning by appointment only. Sunday: 9.30 A.M. to 1.30 P.M.

Confidential

Number of patients respond very well after three weeks of therapy.

Recurrences of Polyposis after functional endoscopic sinus surgery is markedly reduced. Eye Itching, Crusting and nasal bleed as noted with earlier preparations is not noted to that much extent.

Of course caution/povidone in diabetics and hypertension patients is required for fear of worsening or inducing fungal pathology. (Though have not found much literature on this issue on the net.)

The combination therapy (Droxase) is gradually tapered off by me in two to three months time.

Occasionally usage is not advised. The entire bottle must be finished for having the best of results.

I hoping the future is bright for the combination and no one signs up to some contraindication or side effect of

DR. MANISH MUNJAL

I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used Beclomethasone, Budesonide, Azelastine, Fluticasone, Mometasone, with oral antihistamines down the line till date.

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There is a response noted within a week in a few patients but the maximum number of patients respond very well after three weeks of therapy.

Recurrences of polyposis after functional endoscopic sinus surgery is markedly reduced. Eye itching, crusting and nasal bleed as noted with earlier preparations is not noted to that much extent of course caution/avoidance in diabetic and hypertensive patients is required for fear of worsening or inducing any fungal pathology (though have not found much literature on the issue on the net).

The combination Therapy (DUONASE) is gradually tapered off by me in two to three months time.

Occasionally usage is not advised. The entire bottle must be finished for having the best of results.

Hoping the future is bright for this combination and no one digs up some contra indication or side effect of this indication.

VATS E.N.T. CENTRE

(दिल्ली सरकार द्वारा पंजीकृत)

69/5, Yamuna Vihar Road, (Road No. 68), Majipur, Delhi-110053

: 229111
Ph. : 229101
: 229111

Dr. Suresh Vats

M.B.B.S., M.S. (ENT)
CONSULTANT EAR, NOSE & THROAT SURGEON
Formerly ENT Surgeon
ST. STEPHEN'S HOSPITAL
LNJP & GB PANT HOSPITAL

डॉ सुरेश वट्स |

एम.बी.बी.एस., एम.एस. (ई.एन.टी.)

काम, नाल व गला दोग विशेषज्ञ एवं सर्वोन्मय : सुधर 10 से 1 तक जान दे से 5 तक

Reimbursable Yash No. 8, No. (संविचार अधिकारी)

Name: Age & Sex: Rel: Date: Ad:

Name:

जिसमा जो कोई Audiometry एवं Speech Therapy

परी. कुप. कुपर 10 से 1 तक जान 7 से 4 तक

PT. Audiogram/ Hearing Assessment

Alred Audiogram

Hearing Aic Test

Speech Assessment

Speech Therapy

Cetole Test

Impatience

Hb TLC, DLO, B.T., C.T.

ESR, MX-100

Blood Sugar Hb, P.M.P., Blood Urea

Urea B.P. A. M.R.

Prothrombin Time Platelet Count

HbA1c, HIV I & II

ASCC (IgE) Nasopharynx for Epithelioma

YDRL, ASLO Test

T3 T4 TSH

Cytology/Smear for AFP

Throat/Neck/Ear/Hand C & B

Blood - RBC & OBT

FNAC

X-Ray Myeloid - Lst. Osteoid/Osteoma

X-Ray PNS - Wrist

X-Ray Naso-Pharynx-soft Tissue (External)

X-Ray Neck soft Tissue - Lateral

X-Ray Coronal Epiph - Lst. & A.P.

X-Ray - Standard Palpation (M.L.L.T.W)

X-Ray Coronal view for of mouth

X-Ray - Submaxillary/Parotid region - Lst. & L.

X-Ray - Internal Auditory Meatus

X-Ray - T.M. Joint Lst. Open & closed jaw

X-Ray - Nasal Bones - Lateral

X-Ray - Skull - A.P. - Lateral

X-Ray - Chest R.A. View

Barium Sialogram

C.T. Scan - PNS - Cervical 3 mm cuts

C.T. Scan - Temporal bones

C.T. Scan - Neck - Head

P.C.G.

R - L

Rinne's
Weber's

M/L Exa.:



Right Left



Due nose nasal flora
 is unique distinct for
 is available nasal flora
 due to it combined but
 allergic & antinflammatory
 property. It is an anti
 product, effective in the
 patients of Allergic
 Rhinitis with or w/o
 concomitant bronchitis

Allosgli: Worth trying to say
to use in certain patients the
oral anti histamine may be helpful

12/18/08

Dr. SUJESSE VATS
Sr. CONSULTANT M.S. (ENT)
Sr. THROAT SURGEON, M.S.
Reg. No. MCI-2102, DMC-112
698/5, Row No. 66, Mahavir Encl. 53

Dr. SURESH VATS

Duonase Nasal spray is unique & distinct from other available nasal sprays due to its combined Anti-allergic & anti-inflammatory properties. It is an excellent product, effective in majority of patients with allergic Rhinitis with or without concomitant Bronchial Allergy. Worth Trying. Safe to use in certain patients where oral antihistamine may be harmful.

डॉ. बी. बी. माथुर
रम. डी.

वरिष्ठ विशेषज्ञ एवं एसोसिएट प्रोफेसर
मेड. एवं टी.बी. विभाग
सरकारी एडिकल कॉलेज, बीकानेर
RMC No. 7468

Dr. B. B. Mathur
M.D.

Senior Consultant & Associate Professor
Chest & T.B., Hospital
S.P. Medical College, BIKANER
O Hos. :0151-2226333, Res. 0151-2528789

Ref No.

Date... 17/8/05

1) Unhaze Nasal Spray is highly effective in controlling symptoms and subsequent relapse in patients of Allergic Rhinitis. I have used this product in many patients and due to its efficacy it gives confidence to patients to take care of symptoms due to rapid onset of anti-inflammatory action and long lasting relief due to anti-inflammatory action.

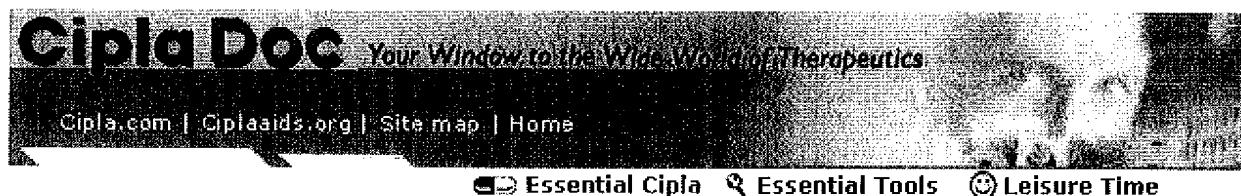
1

Dr. B. B. Mathur
डॉ. बी. बी. माथुर
सरकारी एडिकल कॉलेज
सी. बी. एम. सी. एम. विभाग
सरकारी एडिकल कॉलेज
बीकानेर (राज.)



Dr. B.B. MATHUR

Duonase Nasal spray is highly effective in controlling symptoms and subsequent relapse in patients of Allergic Rhinitis. I have used this product in many patients and due to its efficacy it gives confidence to patients as it takes care of symptoms due to rapid onset of action and long lasting relief due to anti-inflammatory action.

Exhibit C

Cipla

Therapeutic Index

Nasal Preparations

Duonase Nasal Spray

Azelastine hydrochloride & Fluticasone propionate

Each spray delivers

Azelastine hydrochloride BP 140 mcg
Fluticasone propionate BP 50 mcg

Composition

Fluticasone propionate BP 0.0357% w/v
Azelastine Hydrochloride BP 0.10% w/v
Benzalkonium Chloride NF 0.01% w/v
(as preservative)
Phenyl Ethyl alcohol USP 0.25% v/v
(as preservative)

Description

Duonase is an antihistamine-corticosteroid combination available as a metered spray formulation for intranasal administration. It contains azelastine hydrochloride, which is a s generation H 1 receptor antagonist with potent topical activity and fluticasone propionate, synthetic corticosteroid with anti-inflammatory properties.

Pharmacology

As Duonase is a combination of Azelastine and Fluticasone; the pharmacological properties of both the molecules are given separately.

Pharmacology of Azelastine Hydrochloride

Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H 1 -receptor antagonist activity in isolated tissues, animal models, and humans. The major metabolite, desmethylazelastine, also possesses H 1 -receptor antagonist activity.

Pharmacokinetics and Metabolism

After intranasal administration, the systemic bioavailability of azelastine hydrochloride is approximately 40%. Maximum plasma concentrations (C_{max}) are achieved in 2-3 hours. On intravenous and oral administration, the elimination half-life, steady-state volume of distribution, and plasma clearance are 22 hours, 14.5 L/kg, and 0.5 L/h/kg, respectively. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted in the feces with less than 10% as unchanged azelastine. Azelastine is oxidatively metabolized to its principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. Specific P450 isoforms responsible for the biotransformation of azelastine have not been identified; however, clinical interaction studies with the known CYP3A4 inhibitor erythromycin failed to demonstrate a pharmacokinetic interaction. In a multiple-dose, steady-state drug interaction study in normal volunteers, cimelidine (400 mg twice daily), a nonspecific P450 inhibitor, raised orally administered mean azelastine (4 mg twice daily) concentrations by approximately 65%.

The major active metabolite, desmethylazelastine, was not measurable (below assay limit) after a single-dose intranasal administration of azelastine hydrochloride. After intranasal dosing of azelastine hydrochloride to steady-state, plasma concentrations of desmethylazelastine reached

from 20-50% of azelastine concentrations. When azelastine hydrochloride is administered, desmethylazelastine has an elimination half-life of 54 hours. Limited data indicate that the metabolite profile is similar when azelastine hydrochloride is administered via the intranasal route.

Pharmacology of Fluticasone Propionate

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity.

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to natural hormone. However, the clinical significance of these findings in relation to the low levels is not known.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

Pharmacokinetics:

Absorption: Fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (1 pg/mL) only when recommended doses were exceeded and then only in occasional samples at low plasma levels. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral or radiolabeled drug have demonstrated that fluticasone propionate is highly extracted from plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circulating radioactivity is due to an inactive metabolite.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 91% with a linear, obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is not significantly bound to human transferrin.

Metabolism: The total blood clearance of fluticasone propionate is high (average, 1,050 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulatory metabolite detected in man is the 17(beta)-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This inactive metabolite had a 100-fold lower affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human hepatoma cells in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of the radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Indications

Duonase is indicated for the management of symptoms of allergic rhinitis once the need for an antihistamine and corticosteroid has been established. It is recommended to treat **moderate to severe persistent symptoms** in adults above 12 years. For children above 5 years, **Duonase** is recommended for **severe symptoms** of allergic rhinitis. **Duonase** can be used for treating non-allergic vasomotor rhinitis in adults and children 12 years of age and older.

Dosage And Method of Administration

Adults and children 5 years and older: 1 spray/nostril twice daily

The recommended dosage should not be exceeded. Not recommended for use in children under 5 years.

Contraindications

Duonase is contraindicated in patients with or known hypersensitivity to azelastine hydrochloride or fluticasone propionate or any of the components of the preparation.

Warnings and Precautions

- Concurrent use of this combination with alcohol or other CNS depressants or other antihistamines should be avoided as additional reductions in alertness and additional impairment of CNS performance may occur due to azelastine.
- The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. Some patients may experience symptoms of withdrawal e.g. joint and/or muscular pain, lassitude and depression.
- The concomitant use of an intranasal corticosteroid with other corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis. Therefore the combination should be used cautiously in patients with other pathological conditions requiring steroids.
- Intranasal corticosteroids may cause a reduction in growth velocity when administered at higher doses. The recommended dosage of **Duonase** should not be exceeded.
- Special care is needed in patients with lung tuberculosis and fungal and viral infections. Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles for example can have a more serious and a fatal course in children on immunosuppressant corticosteroids.
- During long term therapy, monitoring of hematological and adrenal function is advised.
- In clinical studies with intranasal fluticasone propionate, the development of localized infections of the nose and the pharynx with *Candida albicans* has been seen rarely. If such an infection develops, it may require treatment with appropriate local therapy and discontinuation of the treatment with **Duonase** is advised.

Drug Interactions

The use of **Duonase** in patients taking concurrent drugs, which are potent inhibitors of the cytochrome 450 3A4 system e.g. Ketoconazole and protease inhibitors such as ritonavir may be associated with increased systemic exposure of fluticasone.

Pregnancy

The combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

It is not known whether azelastine hydrochloride or fluticasone propionate is excreted in human milk. Hence, caution should be exercised while prescribing this combination to nursing mothers.

Undesirable Effects

The most likely side effects with this combination are headache, somnolence, pharyngitis, epistaxis, nasal burning/irritation, nausea, vomiting, cough, taste disturbance. The combination may produce a bitter taste, which may lead to occasional nausea. Bitter taste disappears sometime.

Shelf Life

2 years

Storage and Handling Instructions

Store below 30°C.

Do not refrigerate.

Protect from direct sunlight.

Packaging Information**Duonase Nasal Spray**

Sales pack contains 70 metered doses

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Sr. No	TEST	FLUTICASONE PROPIONATE AQUEOUS NASAL SPRAY
1	ASSAY	Preparation of Mobile Phase
		Acetonitrile, Ammonium phosphate buffer pH 3.5 and methanol in the ratio of 15:35:50.
		Column
		A stainless steel column 15 cm X 4.6 mm internal diameter packed with octadecylsilyl silica gel for chromatography (5 μ m)
		Flow rate
		About 1.5 ml/min
		Detection wavelength
		239nm
		Column oven temperature
		40°C
2	RELATED SUBSTANCES	Retention time
		About 6.5minutes
		Run time
		10 minutes
		Injection volume
		100 μ l of each solution
		Diluent
		Mobile Phase
		Standard preparation
		1ppm Fluticasone propionate
		Sample preparation
		1ppm Fluticasone propionate
		Preparation of Mobile Phase A
		Acetonitrile and methanol (97: 3)
		Preparation of Mobile Phase B
		Water, methanol and Orthophosphoric acid (97: 3: 0.1)
		Column
		15 cm X 4.6mm column that contains 5 μ packing L1 with guard column 50mm X 4.6mm, 5 μ packing L1
		Flow rate
		1.5 ml/min
		Detection wavelength
		239nm
		Column oven temperature
		40°C
		Run time
		70 minutes
		Injection volume
		100 μ l
		Diluent
		Distilled Water: Acetonitrile (50:50)
		Standard preparation
		100ppm Fluticasone propionate
		Reference preparation
		1ppm Fluticasone propionate
		Sample preparation
		100ppm Fluticasone propionate
		Impurities monitored
		Fluticasone acid propionate
		Fluticasone acetate
		S-methyl Fluticasone
		Chloro Fluticasone
		Iodo Fluticasone

Sr. No	TEST	AZELASTINE HYDROCHLORIDE NASAL SPRAY
1	ASSAY	Preparation of Mobile Phase Methanol, Ammonium phosphate Buffer and Acetonitrile in the ratio of (450:400:150), 1ml of Triethylamine, pH = 5.0
		Column Octadecylsilyl C18, 25 cm X 4.6mm, 5µm column
		Flow rate About 1.2 ml/min
		Detection wavelength 290nm
		Column oven temperature 25°C
		Retention time About 6.0 minutes
		Run time 10.0 minutes
		Injection volume 20µl
		Diluent Buffer : Acetonitrile: Methanol (350:350:300)
		Standard preparation 50ppm Azelastine HCl
2	RELATED SUBSTANCES	Sample preparation 50ppm Azelastine HCl
		Preparation of Mobile Phase A Ammonium phosphate buffer, Acetonitrile, Methanol in the ratio of (510:140:350); adjust pH to 5.0 with 1ml of triethylamine
		Preparation of Mobile Phase B Ammonium phosphate buffer, Acetonitrile, Methanol in the ratio of (300:300:400); adjust pH to 5.0 with 1ml of triethylamine
		Column 15 cm X 4.6mm column that contains 5µ packing L1 with 20mm X 4.0mm, guard of packing L1.
		Flow rate 1.0ml/min
		Detection wavelength 290nm
		Column oven temperature 40°C
		Run time 60 minutes
		Injection volume 50µl of each solution
		Diluent Buffer : Acetonitrile: Methanol { 350:350:300}
		Standard preparation 250ppm Azelastine HCl
		Reference preparation 2.5ppm Azelastine HCl
		Sample preparation 250ppm Azelastine HCl
		Impurities monitored N-oxide A
		N-oxide B
		Impurity D

Sr. No	TEST	AZELASTINE HYDROCHLORIDE AND FLUTICASONE PROPIONATE NASAL SPRAY	
1	ASSAY	Preparation of Buffer solution	0.01M Ammonium dihydrogen orthophosphate, pH 3.5 with dilute orthophosphoric acid
		Preparation of Mobile Phase	Methanol : Buffer solution : Acetonitrile (500 : 350 : 150)
		Column	C8, 25 cm x 4.6mm, 5 μ m
		Flow rate	1.5 ml/min
		Detection wavelength	239 nm
		Column oven temperature	40°C
		Injection volume	20 μ l
		Standard preparation	For Azelastine hydrochloride: about 50 ppm For Fluticasone propionate: about 18 ppm
		Sample preparation	For Azelastine hydrochloride: about 50 ppm For Fluticasone propionate: about 18 ppm
2	RELATED SUBSTANCES		Azelastine HCl
		Preparation of Mobile Phase A	0.01M Ammonium dihydrogen phosphate, pH 3.5 with orthophosphoric acid
		Preparation of Mobile Phase B	Acetonitrile and Methanol (1:1)
		Column	C18, 25cm x 4.6mm, 5 μ m
		Flow rate	1.0ml/min
		Detection wavelength	239nm
		Column oven temperature	40°C
		Injection volume	10 μ l of each solution
		Diluent	Methanol
		Standard preparation	About 500 ppm Azelastine HCl
		Reference preparation	About 1 ppm Azelastine HCl
		Sample preparation	About 500 ppm Azelastine HCl
		Impurities monitored	1-methyl-4-2-(benzoylhydrazino) azepan Impurity A - 6 α ,9-difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17-(propanoyloxy) androsta-1,4-diene-17 β -carboxylic acid Impurity B - 16 α ,9-difluoro-11 β -hydroxy-16 α -

	yl]carbonyl]suiphenic acid
	Impurity C - $6\alpha,9$ -difluoro-17-[[[(fluoromethyl)sulphanyl]carbonyl]-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-dien-17 α -yl acetate
	Impurity D - $6\alpha,9$ -difluoro-17-[[[(methylsulphanyl)carbonyl]-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-dien-17 α -yl propanoate
	Impurity E - $6\alpha,9$ -difluoro-17-[[[(fluoromethyl)sulphanyl]carbonyl]-11 β -hydroxy-16 α -methyl-3-oxoandrosta-4-en-17 α -yl propanoate
	Impurity F - $6\alpha,9$ -difluoro-17-[[[(fluoromethyl)sulphanyl]carbonyl]-16 α -methyl-3,11-dioxoandrosta-1,4-dien-17 α -yl propanoate
	Impurity G - $6\alpha,9$ -difluoro-17-[[[(fluoromethyl)sulphanyl]carbonyl]-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-dien-17 α -yl $6\alpha,9$ -difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate
	Impurity H - 17,17'-(disulphanediyl dicarbonyl)bis($6\alpha,9$ -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-dien-17 α -yl) dipropanoate
	Impurity I - 7,17'-(trisulphanediyl dicarbonyl)bis($6\alpha,9$ -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-dien-17 α -yl) dipropanoate

Sr. No	TEST	BUDESONIDE NASAL SPRAY
1	ASSAY	Preparation of Mobile Phase Acetonitrile : Distilled water (65 : 35)
		Column C18, 25 cm x 4.6mm, 5 μ m
		Flow rate 2.0 ml/min
		Detection wavelength 242 nm
		Column oven temperature 25°C
		Run time 5 minutes
		Injection volume 20 μ l
		Diluent Mobile phase
		Standard preparation 20 ppm
		Sample preparation 20 ppm
2	RELATED SUBSTANCES	Preparation of Mobile Phase 0.025M Sodium phosphate Buffer pH 3.2 and Acetonitrile in the ratio of (720 :280)
		Column Octadecylsilicagel C18, 25cm x 4.6, 5 μ m
		Flow rate 1.5ml/min
		Detection wavelength 240nm
		Column oven temperature 25°C
		Run time 60 minutes
		Injection volume 20 μ l of each solution
		Diluent Acetonitrile and mobile phase
		Standard preparation 320ppm
		Reference preparation 3.2ppm
		Sample preparation 320ppm
		Desonide (Imp F as per Ph Eur)
		21 - Dehydrobudesonide epimer I (Imp D as per USP)
		21 - Dehydrobudesonide epimer II (Imp D as per USP)

Sr. No	TEST	AZELASTINE + BUDESONIDE NASAL SPRAY	
1	ASSAY	Preparation of Mobile Phase B	0.01M Ammonium phosphate Buffer, Acetonitrile and methanol (300:300: 400)
		Column:	C18, 25 cm x 4.6mm column that contains 5 μ packing
		Flow rate:	1.0 ml/min
		Detection wavelength:	242nm
		Column oven temperature:	45°C
		Run time:	9 minutes
		Injection volume:	20 μ l
		Diluent	Buffer, Acetonitrile and methanol (350:350: 300)
		Standard preparation	20ppm Azelastine 10ppm Budesonide
		Sample preparation	20ppm Azelastine 9.3ppm Budesonide
2	RELATED SUBSTANCES	Preparation of Mobile Phase A	Buffer, Acetonitrile and methanol (51:14: 35)+1 ml of TEA /litre----- pH 5.0 with Orthophosphoric acid
		Preparation of Mobile Phase B	Buffer, Acetonitrile and methanol (30:30: 40)+1 ml of TEA /litre----- pH 5.0 with Orthophosphoric acid
		Buffer	1.15 gm Ammonium dihydrogen ortho phosphate----->1000 ml Distilled water
		Column:	C18, 15 cm X 4.6mm column that contains 5 μ packing with C18 guard column
		Flow rate:	1.0 ml/min
		Detection wavelength:	254nm
		Column oven temperature:	40°C
		Run time:	70 minutes
		Injection volume:	50 μ l
		Diluent	Buffer, Acetonitrile and methanol (35:35: 30)
		Standard preparation	250ppm Azelastine 100ppm Budesonide
		Reference preparation	2.5ppm Azelastine 1ppm Budesonide
		Sample preparation	250ppm Azelastine 117ppm Budesonide
		Impurities monitored	N-oxide A impurity of Azelastine
			N-oxide B impurity of Azelastine
			Impurity D of Azelastine
			Impurity D of Budesonide (as per Ph Eur.)
			Impurity A of Budesonide (as per Ph Eur.)
			Impurity B of Budesonide (as per Ph Eur.)
			Impurity F of Budesonide (as per Ph Eur.)
			Impurity E of Budesonide (as per Ph Eur.)
			Impurity G of Budesonide (as per Ph Eur.)